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Illustrated Atlas of post-AF Ablation Cerebral Abnormalities

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Synopsis

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and relates to high morbidity and mortality due to thromboembolic events, especially ischemic stroke. During the last fifteen years, transcatheter ablation has emerged as an effective therapeutic option to treat AF but carries a risk of possible complications. The occurrence of cerebrovascular accidents, both symptomatic and silent, is one of the most frequent and severe. Transcatheter AF ablation entails a relevant risk of silent cerebral ischemia (SCI) detected by means of Magnetic Resonance Imaging and many efforts have been directed to improve the safety of this procedure.

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias affecting 1-2% of the worldwide population and its burden is expected to rise in the next decades^{1,2}. Prevalence of AF increases with age, from less than 0.4% at 40-50 years of age up to 15% over the age of 80^{3,4}. Independently from the presence of comorbidities, AF relates to enhanced mortality and thromboembolism⁵, particularly to the brain.

The cerebral thromboembolic damage secondary to AF may be clinically overt or appear as a silent phenomenon⁶. If symptomatic brain damage is easily diagnosed and has been thoroughly analyzed, the relationship between AF and silent cerebral ischemia (SCI) needs further evaluation.

SCI have been proven not to be “really silent” from a clinical point of view and to deserve attention by the worldwide medical community, especially as possible complication of transcatheter ablation⁷.

As a matter of fact, the presence of silent cerebral damage resulted in a higher incidence of stroke, physical disability, death and with cognitive function worsening^{8,9,10}. In addition, a recent study¹¹ underlined that the greater SCI burden typical of patients with AF can negatively impact neuro-psychological performance as compared with a control group.

Cerebral ischemia and Atrial fibrillation ablation

During the last fifteen years, transcatheter ablation of AF has emerged as an effective therapeutic option to restore sinus rhythm (SR), relieve symptoms and prevent thromboembolic events in patients refractory or intolerant to antiarrhythmic medications¹².

As any invasive procedure AF ablation carries a risk of possible complications, whose the occurrence of cerebrovascular accidents is one of the most frequent and severe.

If the incidence of clinically relevant brain alterations following AF ablation can reach 0.9%¹³, the occurrence of SCI is much more common and ranges from 7 to 50%. This broad variation can be

attributed to the different patient characteristics, anticoagulation protocol and type of energy used to perform the ablation among different studies¹⁴⁻¹⁷.

Patients clinical characteristics such as age^{18,19}, previous episodes of AF²⁰, presence of pre-ablation SCI²¹, coronary artery disease, left ventricular hypertrophy or dilatation¹⁴ as well as procedural aspects [i.e. intraprocedural cardioversion, activated clotting time (ACT) <250sec⁷, complex fractionated atrial electrograms¹⁸] were associated with the occurrence of SCI following transcatheter ablation.

Being SCI related not only to AF itself but also to AF transcatheter ablation performed indeed to cure this arrhythmia, our group, as other research teams, tested different interventional protocols, ablation tools and energy sources, in order to minimize the occurrence of such complication.

The anatomical features and distribution of SCI occurring following transcatheter ablation represent a crucial and unresolved issue and need to be further investigated. In addition, if these lesions persist or disappear at follow-up^{21,22} and their effective clinical impact remain still unclear and represent a matter of debate²³. Although computed tomography (CT) scans were previously performed to evaluate the possible occurrence of post AF ablation brain alterations²⁴⁻²⁶, more recently, magnetic resonance (MR) imaging has become the preferred technique used to investigate this problem because of its high sensitivity and accuracy.

Accordingly, fruitful collaborations between cardiologists and neuro-radiologists have been started in many centers in order to achieve thorough cerebral MR scans analyses of patients with AF.

The aim of this article is to discuss the current knowledge about post-AF ablation cerebral abnormalities with particular attention towards their MR features.

Research Protocol on Cerebral ischemia following AF ablation

In our experience we examined by means of cerebral MR imaging a large population of about 900 AF patients undergoing AF transcatheter ablation, of which a group resulted that was affected by SCI following this intervention.

In general, in all the studies focusing on cerebral ischemia following AF ablation performed by our group, all patients included were evaluated by the protocol summarized below:

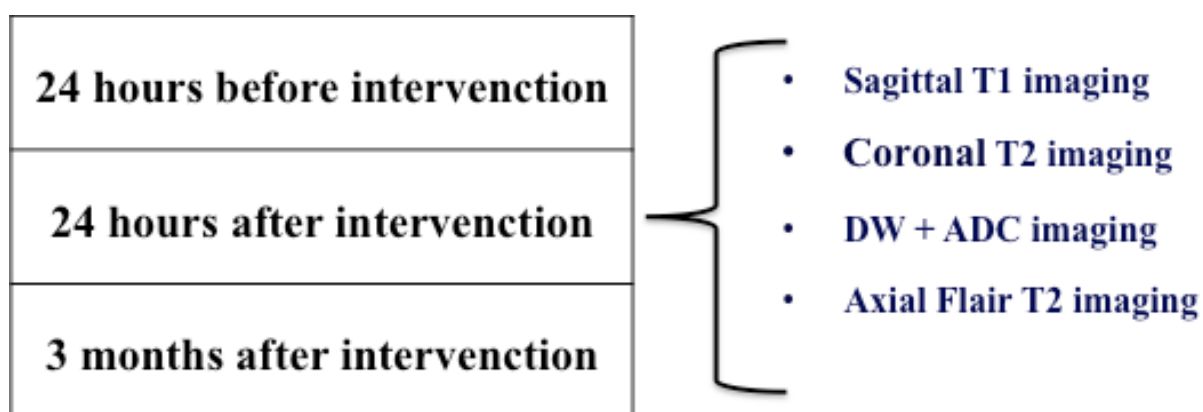
- Medical history (specifically focused on AF subtype and duration, comorbidities and presence of underlying structural heart disease).
- Thromboembolic risk assessment performed by means of systematic calculation of CHADS₂²⁷ and CHA₂DS₂VASc²⁸ scores.
- Pharmacological history (in particular focused on the anticoagulation regimen used).
- Standardized neurological examination based on the National Institute of Health Stroke Scale (NIHSS Scale) administered by certified neurologists (at the time of admission, after the neuroimaging investigation and during follow-up) in order to exclude clinical signs and symptoms suggestive of focal or global deficits.
- Echocardiographic assessment (both transthoracic and transesophageal).
- MR scans were performed one day before and the day following the ablation. All MRI scans were collected and assessed by two certified neuroradiologists blinded to clinical details. Eventually, a sub-group of patients underwent follow-up MR after 3 months.
- Evaluation of cognitive function by means of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)²⁹.
- Different ablation technologies and protocols were evaluated.
- Exclusion criteria have been described elsewhere^{7,11}.

Cerebral MR imaging protocol and definition of cerebral ischemic lesions following AF transcatheter ablation

The imaging protocol used in our center is summarized in Figure 1.

Brain MRI examinations were obtained with a 8-channel head coil on Magnetom Avanto® 1,5 Tesla (Siemens, Erlangen, Germany) following an imaging protocol including a sagittal T1- and Coronal T2-weighted spin echo sequence (repetition time/echo time 400/13 msec) and an axial T2-Fluid Attenuated Inversion Recovery [FLAIR] (repetition time/echo time 8500/112 msec; TI, 2500 msec) scan, with a 240 mm field of view, 5 mm section thickness and 154x256 matrix. A diffusion-weighted (DW) and an ADC (apparent diffusion coefficient) mapping sequences with a single shot spin echo with echo-planar imaging technique (repetition time/echo time 3200/99 msec, field of view 230 mm, matrix 128x128, bandwidth 1502 Hz, gradient strength 22 mT, duration of diffusion gradient 31 msec, gradient separation 42 msec in 3 orthogonal directions, acquisition time 43 seconds) was also used.

Figure 1 Magnetic Resonance Imaging (MR) research protocol; DW: diffusion weighted; ADC: apparent diffusion coefficient.



A standardized definition of AF ablation-related Silent Cerebral Ischemia unfortunately is still lacking. In our studies an acute embolic lesion was defined as a focal hyperintense area on T2-FLAIR sequences or isointense in T1-weighted images, not present at the pre-procedural scan, corresponding to a restricted diffusion signal in the DW sequence and confirmed by ADC mapping to rule out a shine-through artifact⁷.

Peri-vascular spaces were differentiated from small (<3 mm) lacunar ischemic lesions on the basis of their location, form, surrounding gliosis and T2-FLAIR weighted sequences³⁰ (the former appearing as hypointense the latter as hyperintense). Leukoaraiosis was defined as bilateral and either patchy or diffuse areas of hyperintensity on T2- and hypointense on T1-weighted MRI sequences confined to the periventricular regions or extending into the centrum semiovale³¹.

Size and localization of the focal lesions were recorded according the classification showed in Table 1.

Table 1. Anatomical classification and brain distribution of silent cerebral ischemia.

Dimensions	<ul style="list-style-type: none"> • Small (<5 mm) • Medium (≥ 5 and < 10 mm) • Large (≥ 10 mm)
Cerebral Hemisphere	<ul style="list-style-type: none"> • Right hemisphere • Left hemisphere
Brain Region	<ul style="list-style-type: none"> • Frontal lobe • Parietal lobe • Temporal lobe • Occipital lobe • Cerebellum

	<ul style="list-style-type: none"> • Basal ganglia • Nucleus caudatus • Internal capsula • Corpus callosum
Brain tissue depth	<ul style="list-style-type: none"> • Cortical region • Subcortical white matter • Deep white matter

Main findings of the studies

The prevalence of SCI reported in our studies ranges from 5 to 38.9%: more details on SCI incidence and different ablation protocols and techniques tested by our group are given in Table 2.

SCI showed a cortical and bilateral distribution with a typical preferential localization within the context of the parietal and frontal lobes as well as in the cerebellum.

Table 2. Silent cerebral ischemia (SCI) incidence following atrial fibrillation trans-catheter ablation in our different studies. Pts: patients. ACT: activated clotting time; RF: radiofrequency; PVAC: pulmonary veins ablation catheter associated with duty-cycled radiofrequency generator.

Pts (n)	Anticoagulation protocol	Source of energy used	SCI incidence	SCI predictors
232 ⁷ 	Unfractionated Heparin, ACT > 250 sec	Irrigated RF	14.0%	Cardioversion ACT<250 _{sec}
95 ³²	Unfractionated Heparin, ACT > 250 sec	Irrigated RF	6.0%	Cardioversion
80 ³³ 	Unfractionated Heparin, ACT > 300 sec	Irrigated RF, Super irrigated RF	7.5% 5.0%	ACT <320 _{sec}
108 ¹⁵	Unfractionated Heparin, ACT > 300 sec	Irrigated RF Cryoballoon PVAC	8.3% 5.6% 38.9%	PVAC

Atlas of cerebral alterations following AF ablation

The following MR images provide some examples of cerebral alterations occurring in patients with different clinical characteristics after AF transcatether ablation performed with alternative ablation tools.

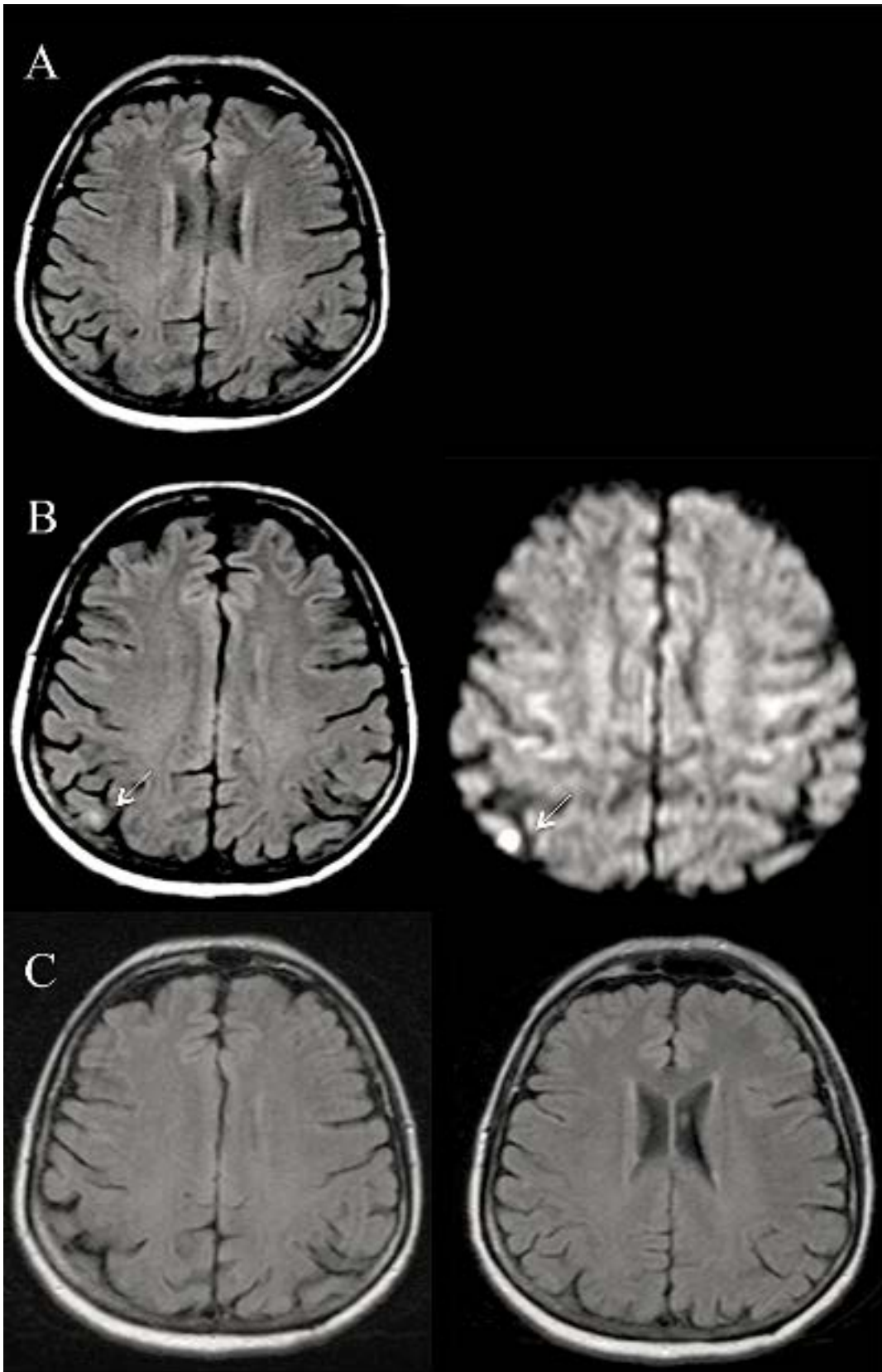
Patient 1

Cerebral MR imaging of a 64 years-old female patient with persistent AF who underwent irrigated RF ablation. (Figure 2).

(A) Pre-procedural scan without brain lesions.

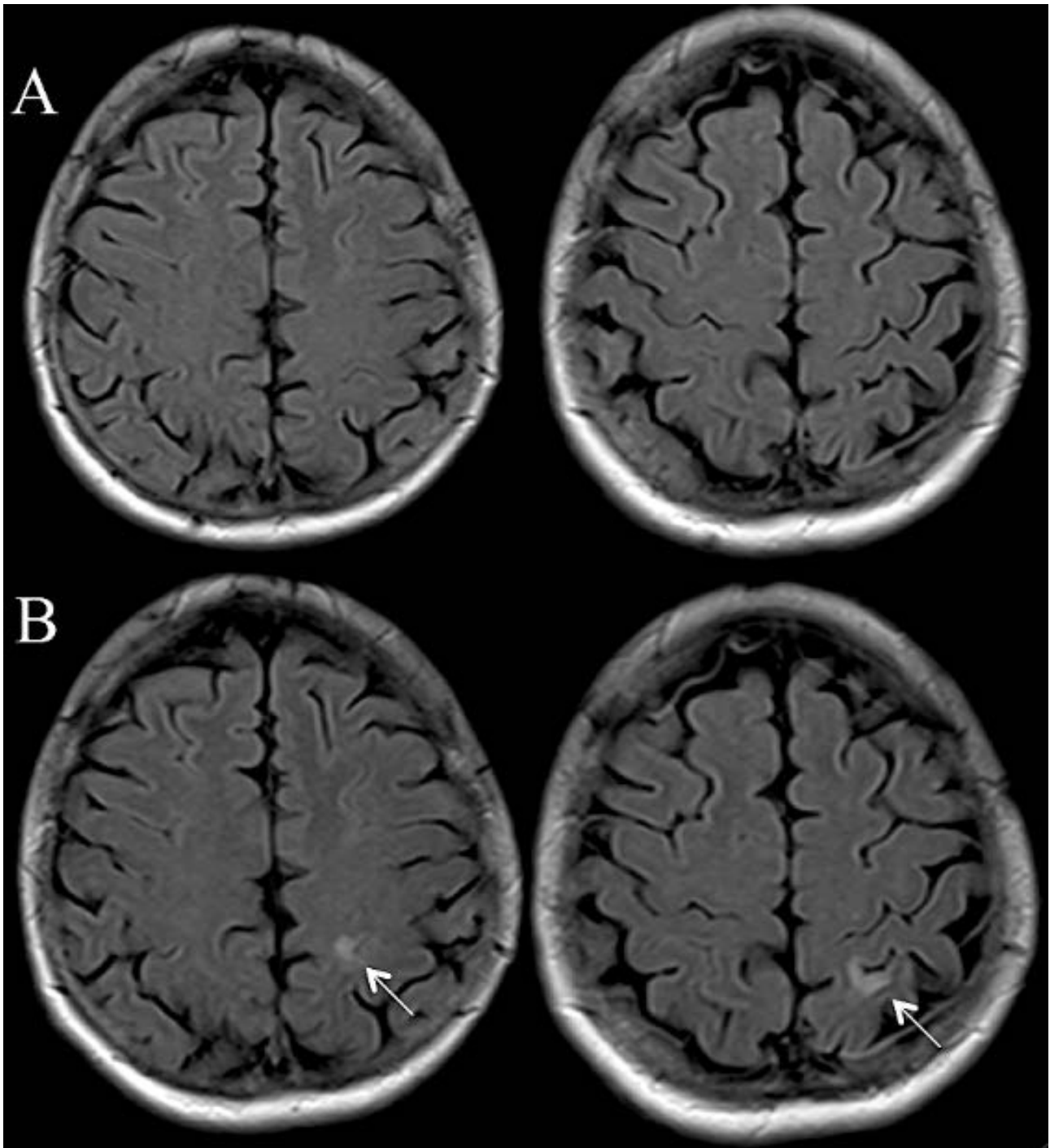
(B) T2- FLAIR and DW images (DWI) post-procedural scans showing the appearance of a single bright cortical lesion in the right parietal lobe (max dimensions 6 x 4 mm) consistent with an acute embolic cerebral infarction (white arrows).

(C) 3 months follow up T2- FLAIR scan demonstrates that the small lesion has disappeared. In order to better visualize the region of interest two adjacent images are provided.



Patient 2

Cerebral MR imaging of 67 years old female patient with paroxysmal AF (Figure 3). MR scans pre (row A) and post RF ablation with PVAC (row B): a new cortical-subcortical single ischemic lesion is present in left parietal lobe (max dimension 10 x 3 mm).

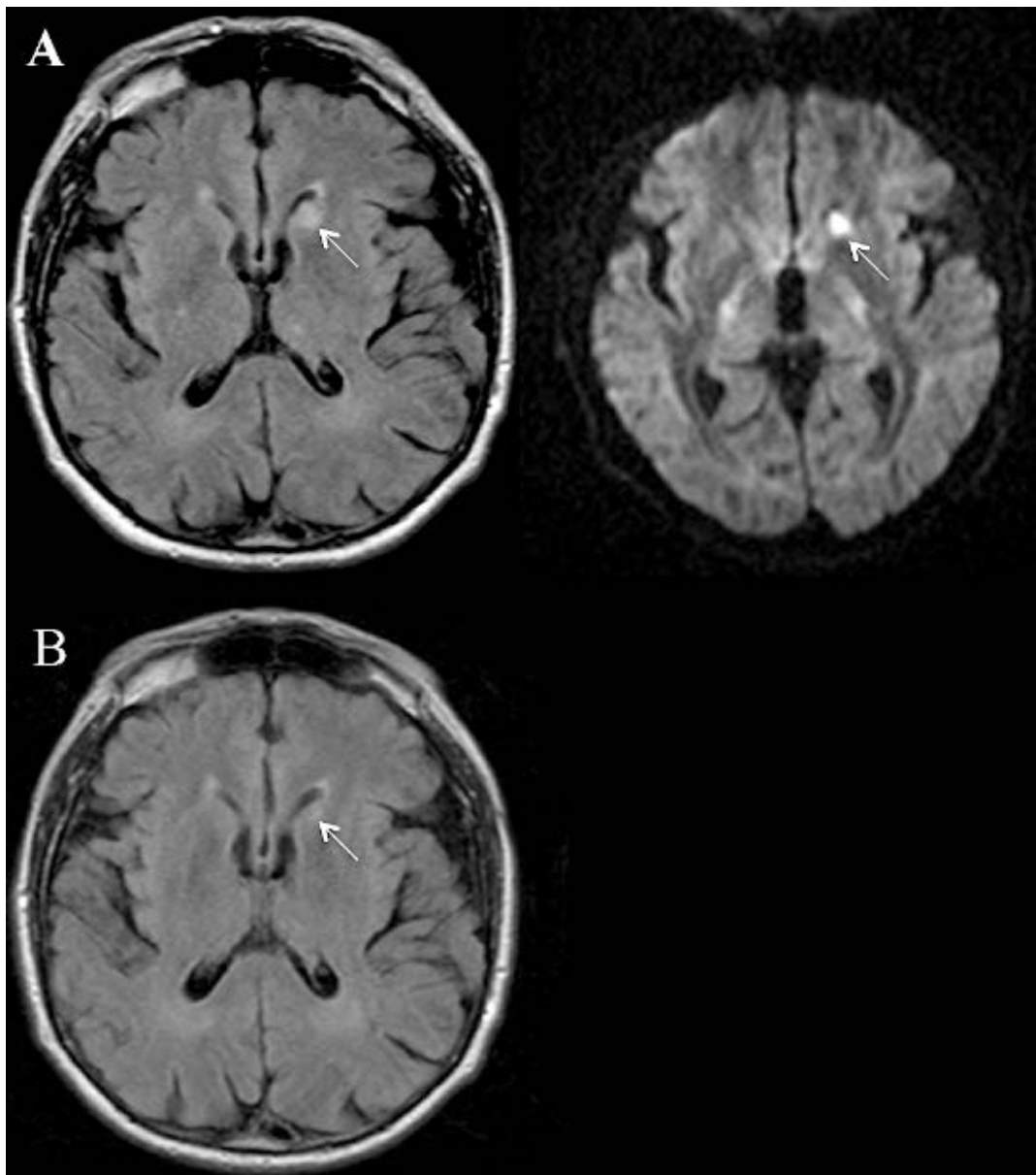


Patient 3

Cerebral MR imaging of a 63 years old male with persistent AF. This is an example of SCI occurring after irrigated RF ablation performed with a mean activated clotting time of 220 sec.

Moreover an electrical cardioversion was administered at the end of this procedure (Figure 4).

Post-procedural cerebral MRI (row A) T2-FLAIR and DW image indicate a single new ischemic lesion in the left head of the caudate nucleus (white arrows) (max dimensions 4 x 4 mm). Three months follow up T2 FLAIR scans (row B) demonstrated the persistence of a lesion of reduced dimensions.

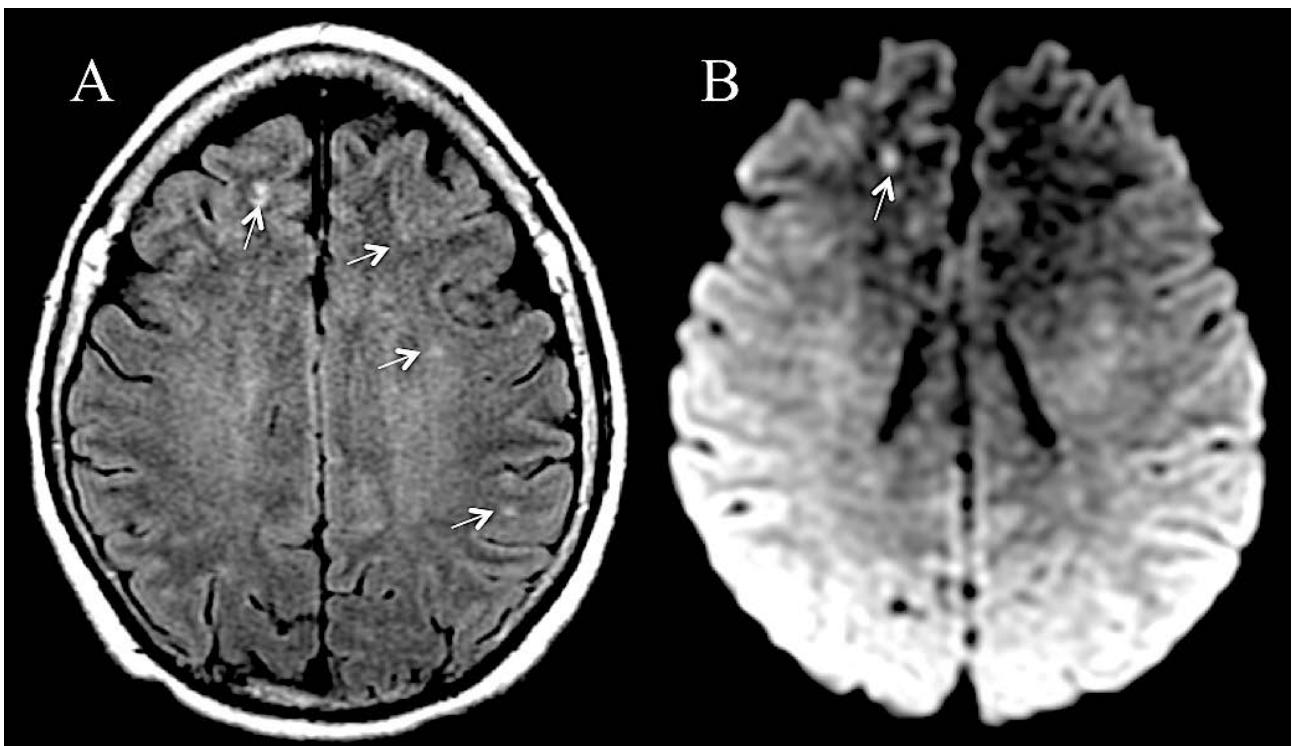


Patient 4

Cerebral MRI of 71 years-old female, with CHA₂DS₂Vasc score 4, who underwent cryoablation for persistent AF (Figure 5).

The T2 FLAIR scan (A) demonstrates multiple cortical-subcortical hyperintense cerebral lesions.

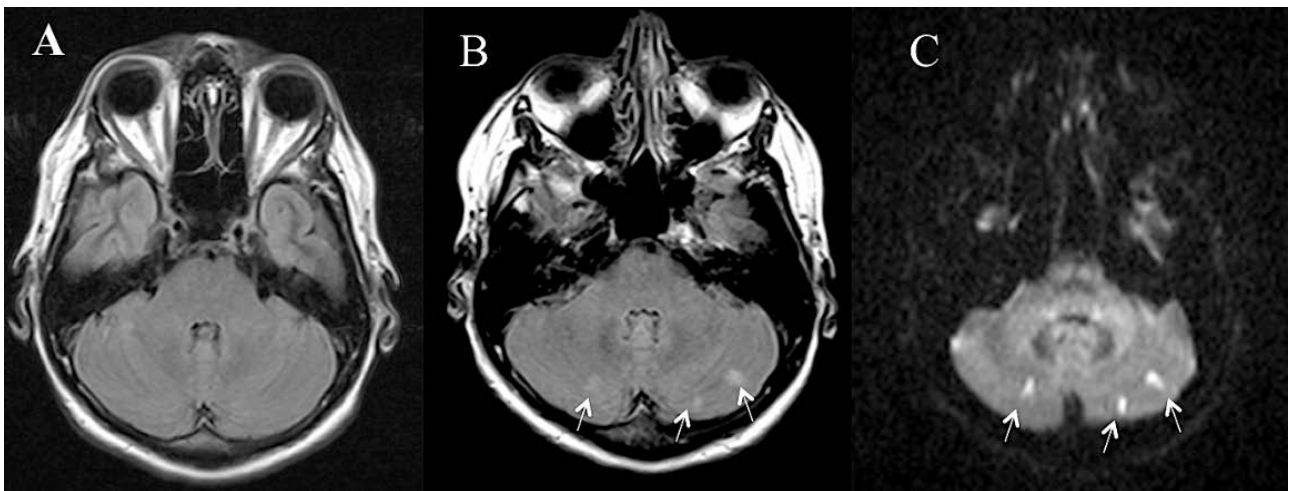
However only one lesions in the superior frontal gyrus (white arrows) is recent as demonstrated in the DW image (B). The other lesions are attributable to older ischemic brain damage.



Patient 5

Multiple new ischemic lesions following irrigated RF ablation are visible in the MR scans of a 54 years old-female patient with paroxysmal AF (Figure 6).

Pre-procedural (A), post-procedural (B) T2 FLAIR and post-procedural DW (C): the white arrows indicate new multiple lesions in the left cerebellum (max dimensions 8 x 6 mm).

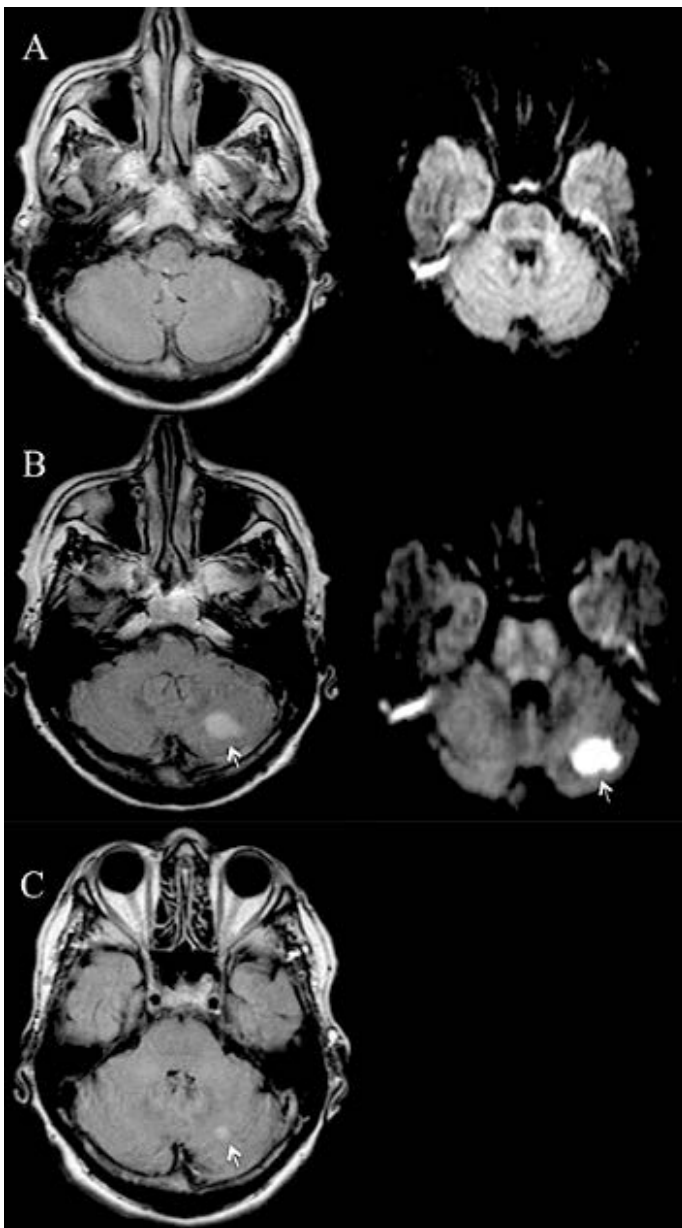


Patient 6

Cerebral MR imaging of a 59 years-old female with paroxysmal AF and hypertension (Figure 7).

In Row A the basal T2 Flair and DWI scans are showed. After irrigated RF ablation (row B) is visible in the right cerebellum a new hyperintense lesion with reduced diffusion (white arrow).

After three months of follow up a smaller lesion is still visible in T2-Flair image (row C).



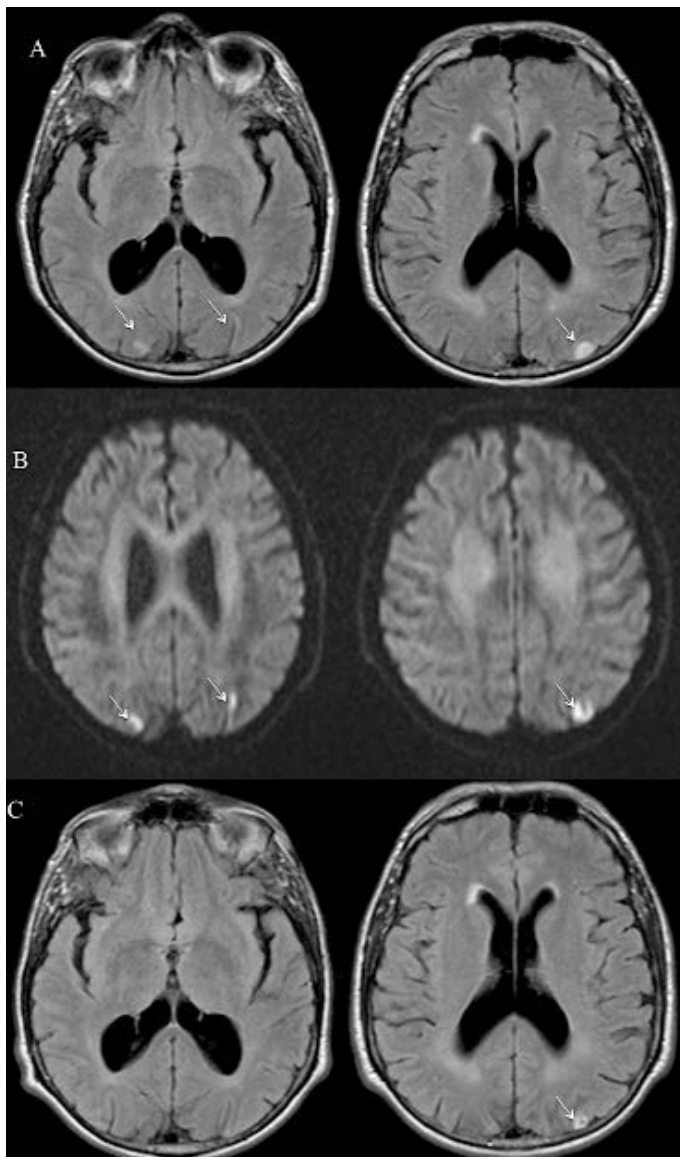
Patient 7

Cerebral scans of 64 years-old male with paroxysmal AF (Figure 8). This is another example of SCI detected after irrigated RF ablation followed by electrical cardioversion at the end of the procedure.

The mean activated clotting time was 250 sec.

Post-procedural (row A) T2-FLAIR and DW image (row B) indicate two new bilateral lesions (max dimensions 20 x 10 mm), the first located in right occipital-parietal lobe and the second in the left parietal lobe.

Three months follow up T2 FLAIR scans (row C) demonstrated the disappearance of the first lesion and a reduction of the second one (white arrows).



Considerations regarding silent cerebral ischemia following atrial fibrillation transcatheter ablation.

In our population experiencing silent cerebral ischemia, following AF transcatheter ablation SCI prevalence ranges from 5 to 38,9%: this broad variation depends on the different ablation protocols and tools utilized (activating clotting time value, electrical cardioversion at the end of procedure, type of energy sources applied). Concerning the pathophysiology of silent embolic lesions, three main mechanisms are responsible for the occurrence of SCI during transcatheter ablation: clot formation, char formation and air/gas embolism. In particular, the following are potential causes of thromboembolism: endothelial disruption, electroporation injury, heating of circulating blood elements^{34,35} and gaseous³⁶ or solid embolism due to catheter movement within the left atria. SCI mostly showed a cortical and bilateral distribution with a typical preferential localization in the parietal and frontal lobes as well as in the cerebellum. These findings are in line with results previously reported by other groups although in smaller study populations. For instance, Schrickel et al¹⁴ outlined a similar distribution of periprocedural cerebral microemboli in the fronto-parietal regions and in the cerebellum in patients with persistent or paroxysmal atrial fibrillation undergoing transcatheter pulmonary vein isolation. The reasons for this preferential localization might be related to the high blood volume and to the vast distribution of the middle cerebral and vertebro-basilar arteries, easily accessed by periprocedural microemboli.

Despite the cortical localization of SCI, none of our patient with post-procedural cerebral alterations had neurological symptoms; this may sound surprising considering that most of the lesions were localized in the cortical region and in the parietal, frontal lobes and cerebellum.

At present the neurocognitive implications of periprocedural SCI still result uncertain and many doubts concerning the persistence or the disappearing of these cerebral lesions at follow up need to be clarified^{21,37,38}.

In particular although a large study showed a lower incidence of cerebrovascular events and dementia among AF patients undergoing RF ablation compared with AF patients not treated with ablation³⁹, other experiences^{22,40} highlighted the presence of some cognitive alterations after this type of interventional procedure.

Although we have some information about the neuropsychological significance of SCI due to AF¹¹ further researches need to be performed in order to fully understand the impact of new cerebral embolic lesions ablation related on cognitive function at long term follow up.

Summary.

Silent cerebral ischemia following transcatheter AF ablation are generally localized in the cortex of the frontal, parietal and cerebellar lobes with about half of the lesions persisting at mid-term follow-up.

It seems to be crucial to continue testing and optimizing AF ablation techniques and protocols in order to reduce their possible embolic complications. In this regard, cerebral MR scans of AF patients has emerged as fundamental evaluation tool.

In addition, it is relevant to create a cardiological and radiological shared knowledge on cerebral damage secondary to AF, being the frequency of these problems already very high and expected to rise in the future decades.

Eventually great attention should be paid to the long-term neurological impact of AF related silent cerebral damage. In the near future, more studies specifically investigating its influence on cognitive function are warranted .

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